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PATENT & TRADEMARK OFFICE

Docket No. 60023 (50152)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Atul Kumar, et al.

SERIAL NO.: **10/677,116**

FILED: September 30, 2003

FOR: (3R,4R)-TRANS-3,4-DIARYLCHROMAN DERIVATIVES AND A METHOD FOR THE PREVENTION AND/OR TREATMENT OF ESTROGEN DEPENDENT DISEASES

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

DECLARATION UNDER 37 C.F.R. 1.132

I, Atul Kumar, a citizen of India residing at Chatter Manzil Palace Lucknow-226 001, Uttar Pradesh, India, hereby declare as follows:

1. I am a co-inventor of the subject matter described and claimed in the patent application U.S.S.N. 10/677,116 filed on September 30, 2003 and otherwise identified above.

2. **Educational Qualification**: MSc. and PhD. (Organic Chemistry).
   Professional Experience: 15 years of experience in medicinal & synthetic organic chemistry and Drug Design

3. I have read and understood the Office Action dated April 5, 2006, and the reference cited in the Office Action: Branham, Phytoestrogens and mycoestrogens bind to the rat uterine Estrogen receptor, J. Nutr. 132:658-664(2002).

4. In relation to claim 21, the reason of choosing RBA is that, Estrogen Receptor relative binding

affinity is an *in vitro* test, which is performed to determine the ER affinity of the test compound towards estrogen receptor via estrogen receptor (ER) competitive binding assay. This RBA is assay (primary Screening test) performed to know quickly weather, compound is binding with ER or not before going to in vivo test. RBA is a very common assay used from many years.

5. Therapeutic /preventive effect by compounds with RBA (5-7): It is very difficult to predict Therapeutic /preventive effect of compound only by RBA data. But a compound having moderate to weak RBA clearly, shows that compound is binding to estrogen receptor. What ever the final effect compound is showing might be through Estrogen receptor.

6. Why that is determined to be effective and that is well accepted in the art to choose the RBA range of 5-7: Literature knowledge about (RBA) shows that RBA (1to 7 or more) is more likely to show biological response. Compounds like Tamoxifen have RBA (5)[1,2] and is a drug for anticancer breast. Beside this compounds like Nafoxidine, Toremifene and Clomiphene have RBA ranges from (0.7 to 1.3)[3] but showing very good biological activity. Compound showing RBA (5-7) have quit good affinity towards estrogen receptor and more likely to show biological response.

7: **References**

(a) **Idoxifene Antagonizes Estradiol-dependent MCF-7 Breast Cancer Xenograft Growth through Sustained Induction of Apoptosis.**

Stephen R. D. Johnston, Irene M. Boeddinghaus, Sharon Riddler, Ben P. Haynes, Ian R. Hardcastle, Martin Rowlands, Rachel Grimshaw, Michael Jarman, and Mitch Dowsett. [**CANCER RESEARCH 59**, 3646–3651, August 1, 1999]

(b) **VC Jordan, RR Bain, RR Brown, B Gosden and MA Santos;** ***Cancer Research*****, Vol 43, Issue 3 1446-1450, 1983**

(c). Robert, M. Blair, Hong Fang, William S. Branham , Hass B.B., Dial S.L , Moland C.L. Wieda Tong Shi L., Roger Perkins, Sheehan D.M. *Toxicology Sciences* 54,138-153 (2000).

8. The reference discussed above showed that person skilled in the art would have the knowledge to determine which compounds would be in the range of specified RBA and what range is well known in the art to be therapeutically effective. Therefore, we (the inventors of the present invention) declare that the present invention concerning the method of prevention and/or treatment, wherein said method helps in preferably diseases or syndromes caused by an estrogen-deficient state, with Relative Binding affinity (RBA) to estrogen receptors ranging between 5 to 7 sufficiently complies with the enablement requirement.

9. I, the undersigned Atul Kumar, further declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 101 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the above identified application or any patent issuing thereon.

By: A Kumar

Atul Kumar

Date: 5·10·2006